Synthesis of Stable 1*H*-Azirines Reinvestigated: A Structural Corrigendum

Klaus Banert,* Manfred Hagedorn, Heiko Peisker

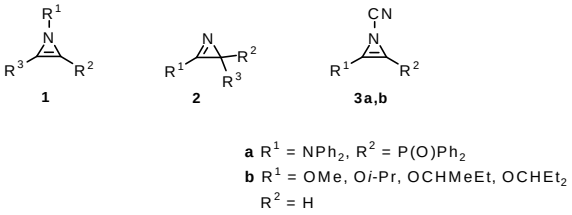
Organic Chemistry, Chemnitz University of Technology, Strasse der Nationen 62, 09111 Chemnitz, Germany
Fax +49(371)53121229; E-mail: klaus.banert@chemie.tu-chemnitz.de

Dedicated to Professor Helmut Quast

Abstract: The isoquinoline-catalyzed synthesis of pretended 1*H*-azirines from phenacyl bromides and *N*,*N*'-dialkylcarbodiimides was repeated. The products do not possess the structure of antiaromatic 1*H*-azirines, but simple *N*-acyl-*N*,*N*'-dialkylureas were formed instead. This structural corrigendum was confirmed by the independent synthesis of the known ureas and comparison of their ^{1}H NMR and ^{13}C NMR spectroscopic data in the case of six compounds. Thus, 1*H*-azirines keep their classification as very short-lived intermediates.

Key words: acylation, antiaromatic heterocycles, structure assignment by spectroscopy, ureas

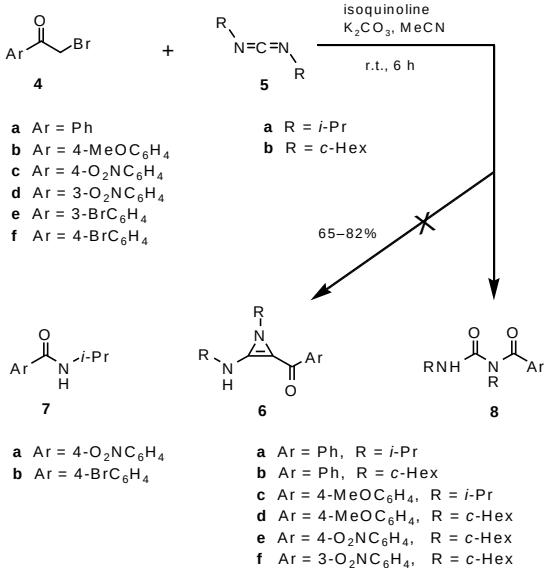
Strained compounds are of special interest because of their increased energy content and the enhanced reactivity, which frequently results from this. For 1*H*-azirines **1** and 2*H*-azirines **2**, it is obvious that both types of heterocycles include considerable ring strain (Scheme 1). However, the properties of **1** and **2** are quite different.[1] A great number of 2*H*-azirines **2**, especially those with $R^1 \neq H$, were isolated and characterized by spectroscopic methods in solution or even by X-ray crystallographic structure determination. Although compounds of type **2** are highly reactive, the 2*H*-azirine unit has been found in a few natural products.[2] On the other hand, only five examples of short-lived 1*H*-azirines **3a**,**b** were photochemically generated and detected at very low temperatures by IR spectroscopy, which indicated absorptions in the region of 1867–1890 cm^{-1} attributed to C=C valence vibration.[3] Most probably, the push-pull substitution pattern of **3a**,**b** diminishes the antiaromatic character of the 1*H*-azirine structure and increases the relative stability. Thus, attempts to isolate or observe the parent compound (**1** with $R^1 = R^2 = R^3 = H$) by cycloaddition[4] or cyclorevision[5] approaches and by using argon-matrix isolation technique were unsuccessful and yielded unsubstituted **2** and other isomeric species. Elusive 1*H*-azirine intermediates were merely postulated in several other reactions, which finally led to 2*H*-azirines,[6] pyrroles,[7] indoles,[8] oxazoles,[9] isoquinolines,[10] ketenimines,[11] nitriles,[12] or anilines.[13] Furthermore, many quantum chemical calculations, that analyzed the energy content,[14] the molecular geometry,[15] the nitrogen inversion barrier,[16] the basicity,[17] and the vibrational frequencies and IR intensities[18] of the parent 1*H*-azirine **1**, have been published. All experimental and theoretical results emphasize the properties of the antiaromatic heterocycles **1** as short-lived intermediates, which cannot be isolated at room temperature.



Scheme 1 Structures of 1*H*-azirines and 2*H*-azirines

Recently, Alizadeh and Rezvanian reported on the synthesis of 1*H*-azirines **6a**–**f** by reaction of phenacyl bromides **4a**–**d** with carbodiimides **5a**,**b** in the presence of potassium carbonate and a catalytic amount of isoquinoline (10 mol%) in anhydrous acetonitrile (Scheme 2).[19] The products **6a**–**f** were isolated by chromatography in 65–82% yield as yellow powders and characterized by their sharp melting points (150–176 °C), IR, ^{1}H NMR, ^{13}C NMR and MS data as well as elemental analyses. It was claimed that the antiaromatic heterocycles **6** were formed from **4** and **5** in 35–64% yield even when protic ethanol was used as solvent and strong bases such as potassium hydroxide were utilized. Surprisingly, phenacyl bromide **4e** did not give any product of type **6** after treatment with **5a** or **5b**, and the reaction of **4c** or **4f** with **5a** exclusively led to the simple amides **7a** or **7b**, respectively (yields: 78–80%).[19]

We had strong doubts about the antiaromatic structures **6** because the corresponding substances obviously are stable at room temperature, which is absolutely incompatible with 1*H*-azirine moieties.[1,3–18] The heterocycles **6a**–**f** should be even less stable than **3a**,**b** since the electron-withdrawing cyano group of **3** is replaced in **6** by an electron-releasing alkyl group that emphasizes the antiaromatic character of the three-membered ring. Moreover, 1*H*-azirines of type **6** should cause IR signals similar to those of **3a**,**b**. But IR absorptions within or near to the region of 1867–1890 cm^{-1} were not found for **6a**–**f**.



Scheme 2 Synthesis of 1*H*-azirines **6a**–**f** reported in ref.[19] and the corrected structures **8a**–**f** of the products from **4** and **5**

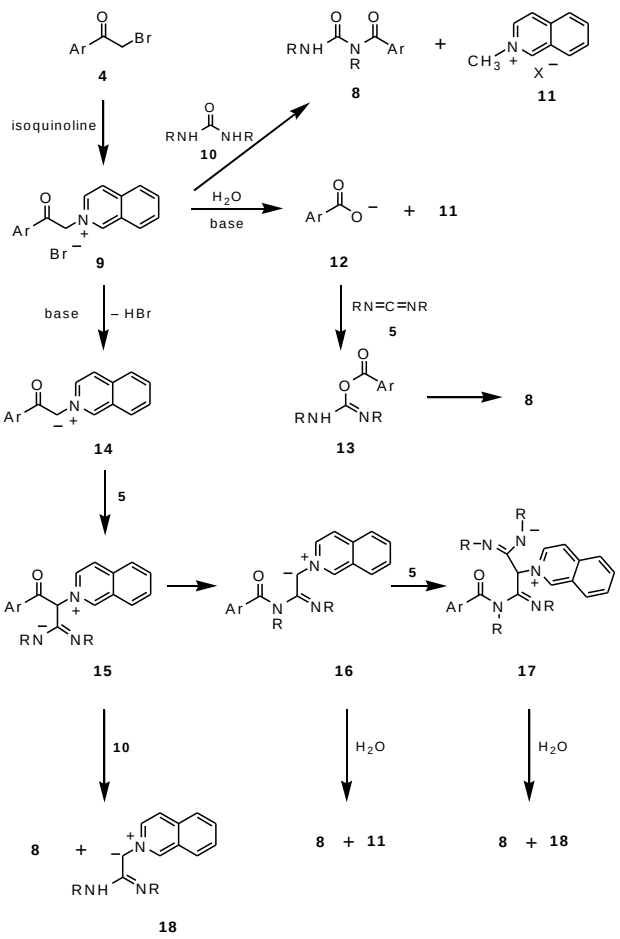
Table 1 Comparison of ^{13}C NMR Data[a] of the Product from **4b** and **5a** with those of **8c**[20]

Product from **4b** and **5a**, ref.[19]	Product from **4b** and **5a**, this work	**8c**,[b] this work
20.95	20.94	20.91
22.33	22.32	22.29
42.70	42.69	42.67
50.24	50.18	50.11
55.42	55.42	55.39
113.85	113.81	113.78
122.11	X	X
128.87	128.87	128.84
X	129.17	129.16
133.24	X	X
154.20	154.54	154 51
161.78	161.74	161.71
172.05	172.03	171.93

[a]Measured in $CDCl_3$, δ values.
[b]Prepared from 4-methoxybenzoic acid and **5a** as described in ref.[21]

When we repeated the reaction of **4a**–**d** with **5a**,**b**, we obtained substances with ^{1}H NMR data which were identical with those reported[19] for **6a**–**f**. Nearly the same was true for the corresponding ^{13}C NMR spectra. In each of the six cases, however, our ^{13}C NMR data sets included one quaternary carbon signal less if compared to the ^{13}C NMR spectra published[19] by Alizadeh and Rezvanian. This is shown in Table 1 for the example[20] of the product from **4b** and **5a** that obviously cannot have the structure **6c**. Our corrected ^{13}C NMR spectroscopic data excluded the 1*H*-azirines **6a**–**f** and led to the alternative structures **8a**–**f**. These *N*-acylureas were described in literature,[21] and in the cases **8a**,**c**,**d** not only ^{1}H NMR but also ^{13}C NMR spectra were reported.[21a,b] We prepared **8a**–**f** for comparison by known procedures and found that ^{1}H NMR and ^{13}C NMR data were identical with those of the products **8a**–**f** synthesized from **4a**–**d** and **5a**,**b**.[20]

Scheme 3 Some of the possible reaction mechanisms



to explain the formation of **8**

The intermediates **9**, **14**, and **15** were used to interpret the generation of the alleged 1*H*-azirines **6**, and the ylides **16** were discussed as precursors, which lead to the amides **7a**,**b** by hydrolysis (Scheme 3).[19] However, these intermediates should alternatively play a role in the formation of **8** from **4** and **5** with loss of one carbon atom. Several reaction mechanisms can be taken into consideration to explain this result. The most simple sequence includes *N*-alkylation of

isoquinoline by **4** and nucleophilic attack of ureas **10**, which are the hydrolysis products of **5**, at the carbonyl group of **9**. This would produce **8** and the salt **11** (X = Br) via the corresponding isoquinolinium ylide. We found that an anhydrous solvent (acetonitrile) is not necessary to prepare **8** from **4** and **5**, and addition of *N*,*N*'-dicyclohexylurea or one equivalent of water did not prevent the formation of **8**. But no **8d** was observed from **4b** when the co-reactant **5b** was completely exchanged by the corresponding urea. Consequently, carbodiimides **5** are essential to synthesize **8** from **4**.

Cleavage of *N*-phenacylpyridinium salts in aqueous alkaline solution is known for 125 years and can be performed under mild conditions to get benzoic acids and *N*-methylpyridinium salts in good yields.[22] This reaction was intensively investigated,[23] utilized in synthesis,[24] and also transferred to the corresponding quinolinium[22a] and isoquinolinium[25] salts. Thus, a plausible mechanism to explain the formation of **8** from **4** and **5** includes cleavage of **9** to generate **11** and the benzoates **12**, which can add to **5**. The resulting O-acylisoureas **13** are able to undergo a Mumm-like rearrangement to yield **8**. It is well known that treatment of benzoic acids with **5a**,**b** leads to *N*-acylureas beside the corresponding benzoic anhydrides.[21c–e,26]

In an alternative reaction mechanism, base-induced transformation of the salts **9** into the stabilized ylides **14** followed by nucleophilic addition at **5** should produce the intermediates **15**. Nucleophilic attack of **10** at the carbonyl group of **15** can yield **8** and the stabilized ylides **18**. On the other hand, intramolecular attack of the NR unit at the carbonyl group of **15** would initiate *N*-acylation and formation of the stabilized ylides **16**. The latter can be hydrolyzed to give **8** and **11**. If **16** adds to a second molecule of **5**, the resulting intermediates **17** should lead to **8** and **18** on hydrolysis.

In summary, we have demonstrated that the reaction of bromides **4** and carbodiimides **5** does not give products with energetic 1*H*-azirine moieties. Consequently, these antiaromatic heterocycles keep their classification as very elusive short-lived intermediates. Instead of alleged 1*H*-azirines **6**, simple *N*-acyl-*N*,*N*'-dialkylureas **8** were generated from **4** and **5**. The formation of these products is surprising but can be explained by several reaction mechanisms.

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